

①

ADA126379

Correlated Morphologic and Functional Studies of
Acute Renal Failure In The Rat

Final Report

Benjamin F. Trump, M.D.

September 1980

Supported by

US ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

Contract No. DAMD17-75-C-5010

University of Maryland
Baltimore, Maryland 21201

DOD DISTRIBUTION STATEMENT

DTIC
ELECTE
APR 05 1983
S D E

Approved for public release; distribution unlimited

DTIC FILE COPY

The findings in this report are not to be construed as an official Department of the
Army position unless so designated by other authorized documents.

83 04 01 021

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER	2. GOVT ACCESSION NO. <i>DA126379</i>	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Correlated Morphologic and Functional Studies of Acute Renal Failure In The Rat		5. TYPE OF REPORT & PERIOD COVERED Final-1 Jul. 1974- 31 Mar. 1976
		6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) Benjamin F. Trump, M.D.		8. CONTRACT OR GRANT NUMBER(s) DAMD17-75-C-5010
9. PERFORMING ORGANIZATION NAME AND ADDRESS University of Maryland School of Medicine Baltimore, Maryland 21201		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 61102A.3A1611012B71R.00.014
11. CONTROLLING OFFICE NAME AND ADDRESS US Army Medical Research and Development Command Fort Detrick Frederick, Maryland 21701		12. REPORT DATE September 1980
		13. NUMBER OF PAGES 9
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		15. SECURITY CLASS. (of this report) Unclassified
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE
16. DISTRIBUTION STATEMENT (of this Report) Approved for public release; distribution unlimited		
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)		
18. SUPPLEMENTARY NOTES		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number)		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number)		

FINAL REPORT

TITLE: CORRELATED MORPHOLOGIC AND
FUNCTIONAL STUDIES OF ACUTE
RENAL FAILURE IN THE RAT

CONTRACT NUMBER: DAMD-17-75-C-5010

PRINCIPAL INVESTIGATOR: Benjamin F. Trump
Professor and Chairman
Department of Pathology
University of Maryland
School of Medicine
10 South Pine Street
Baltimore, Maryland 21201

TELEPHONE NUMBER: Area Code: 301 - 528-7070

ORGANIZATION: University of Maryland
School of Medicine
Department of Pathology
10 South Pine Street
Baltimore, Maryland 21201

Accession For	
HTIS GRAB	X
DTIC TAB	
Unannounced	
Justification	
By _____	
Distribution/	
Availability Codes	
Dist	Avail and/or Special
A	

Over the past several years our laboratory has made significant contributions to the understanding of the mechanisms involved in the initiation of acute renal failure (ARF). These studies have strongly emphasized the correlation of structural and functional alterations following the administration of a nephrotoxic dose (4 mg/kg s.c.) of mercuric chloride (HgCl_2). The results of these studies have been published as individual papers in a five part series.

In the first of these papers, McDowell et al. examined the structural-functional correlation of proximal tubular damage following HgCl_2 administration. The authors showed that all segments of the proximal tubule underwent initial sublethal changes. Despite the widespread nature of these early changes, the injury progressed to necrosis by 24 hrs in only the pars recta (P_3) segment of the proximal tubule. The functional studies performed at 6 hrs, however, revealed that renal failure was already established at this time. This finding disassociates the tubular necrosis seen in the P_3 segment from the initiation of ARF, thereby minimizing the role played by tubular obstruction and back-leak in this model. It was suggested by the authors that the early sublethal changes in the first (P_1) and second (P_2) segments may result in a greatly diminished sodium reabsorption and may be related to the pathogenesis of ARF through a previously proposed feedback mechanism involving the macula densa and renin release. According to this hypothesis, an increased NaCl concentration at the macula densa results in activation of a tubulo-glomerular feedback phenomenon involving renin release with resulting angiotensin II production. Such a mechanism could result in the decreased glomerular filtration rate (GFR), associated with ARF, by an angiotensin-induced

vasoconstriction of the afferent arteriole.

In the second paper, Zalme et al. examined 9 enzyme markers using various histochemical techniques in an effort to demonstrate the extent of early tubular changes following HgCl_2 administration. Decreased activities of alkaline phosphatase and 5'-nucleotidase, two brush border enzymes, were noted as early as 15 min post HgCl_2 injection. This was followed very quickly by a reduction in acid phosphatase, a lysosomal marker. At 6 and 24 hrs all enzymes studied showed decreased activity in all segments of the proximal tubule. Although morphologically the P_1 and P_2 segments of the tubule showed minimal alterations, by 24 hrs severely decreased enzyme activities were observed. These findings are consistent with the hypothesis that sublethal changes occur in both the P_1 and P_2 segments which may result in decreased sodium reabsorption, as described above.

In the third paper, Sato et al. examined the morphological changes in the juxtaglomerular (JG) apparatus following HgCl_2 administration. The authors observed a two-fold increase in the total and deep juxtaglomerular granulation index (JGI) as early as 30 min. An increase in the JGI indicates either a decrease in renin release or increased renin formation. However, by 1 and 6 hrs, clear morphological evidence suggestive of increased renin synthesis was observed, supporting the latter possibility. By 24 hrs, hypergranulation and hypertrophy of the JG cells was noted. The authors propose that the increased JG cell activity may be attributed to activation of the tubuloglomerular feedback phenomenon.

In the fourth and fifth papers (in page proofs), Barnes et al. examined the morphological and histochemical changes associated with two maneuvers previously shown to functionally ameliorate HgCl_2 -induced ARF.

In the first of these studies the protective effect of dithiothreitol (DTT) was examined. DTT, an agent capable of chelating heavy metals, was administered i. p. at a dose of 15.4 mg/kg thirty min following HgCl_2 . Administration of HgCl_2 plus DTT resulted in similar but less severe lesions at 1 hr as did HgCl_2 alone. However, a remarkable protective effect was evident in the P_1 and P_2 segments of the proximal tubule at 3 hrs and throughout the remainder of the study, with virtually no morphological or histochemical changes apparent. Despite the protection seen in the early portions of the tubule, the P_3 segment displayed widespread necrosis as seen in animals receiving HgCl_2 alone. This study again demonstrates the lack of correlation between tubular necrosis of the P_3 segment and the initiation of ARF, and more strongly implicates the role of the sublethal changes in the P_1 and P_2 segments.

In the second of these studies the effect of chronic salt loading on the development of ARF was examined. Chronic salt loading is a method known to result in a decreased renal renin content. Using both morphological and histochemical methods the investigators observed that the administration of HgCl_2 resulted in a similar degree of proximal tubular injury in both salt loaded and water drinking animals; yet the salt loaded animals demonstrated significant functional protection. These findings are in concordance with a renin-angiotensin mediated tubuloglomerular feedback hypothesis. According to this explanation, protection is afforded the chronically salt loaded animals, despite the proximal tubular injury, because the renin depleted animals are incapable of triggering angiotensin production.

In summary, the recent work from our laboratory concerning the pathophysiology of ARF has clarified several important points. We have shown

7

a clear dissociation of tubular necrosis and the initiation of ARF in this model. This finding minimizes the importance of both tubular obstruction and backleak, in the initiation of HgCl_2 -induced ARF. Instead, the importance of the sublethal changes described in the P_1 and P_2 segments is emphasized. We suggest that these changes may result in impaired electrolyte reabsorption which may act as an initiating mechanism via tubuloglomerular feedback. Evidence indicating the involvement of the renin-angiotensin system in such a feedback mechanism has been obtained in the study of Sato et al., and the chronic salt loading experiments of Barnes et al. It should be pointed out, however, that the evidence at this point is circumstantial. Additional work is needed to more clearly evaluate the role of this and/or other vasoconstrictor stimuli.

DISTRIBUTION LIST

12 copies

Director
Walter Reed Army Institute of Research
Walter Reed Army Medical Center
ATTN: SGRD-UWZ-C
Washington, DC 20012

4 copies

Commander
US Army Medical Research and Development Command
ATTN: SGRD-RMS
Fort Detrick, Frederick, MD 21701

12 copies

Defense Technical Information Center (DTIC)
ATTN: DTIC-DDA
Cameron Station
Alexandria, VA 22314

1 copy

Dean
School of Medicine
Uniformed Services University
of the Health Sciences
4301 Jones Bridge Road
Bethesda, MD 20014

1 copy

Commandant
Academy of Health Sciences, US Army
ATTN: AHS-CDM
Fort Sam Houston, TX 78214